REMARKS

Claim Rejections Under 35 USC 112

Claims 1-18 and 20-26 were rejected under 35 USC 112 as being indefinite alleged for reciting that the "third and fourth primers each [have] a sequence homology with the particularly digestible regions of the first and second primers respectively." The Applicants respectfully traverse this rejection. Claims 1 and 20 also recite that the third and fourth primers have a sequence homology ... whereby the third and fourth prier hybridize to the 3' binding regions of the first and second strands respectively." Consequently the third and fourth primer must still be capable of binding to the first and second primers.

The "first" primer is required to hybridize to the 3'-binding region of the target strand. The third primer is required to have sufficient sequence homology with the first primer that it is also capable of binding to (a part of) the 3'-binding region of the target strand. Similar comments apply in relation to the second and fourth primers for the other target strand.

Consider the case described in the penultimate paragraph on page 8, beginning on line 17, of the present specification. The "first" primer is designated as AB (because for convenience it may be considered to have two "sub-sections" A and B). This first primer is also referred to as a "long" primer and is capable of hybridizing to the 3'-binding region of one target strand. The "third" primer is designated as A referring to the "A sub-section" of the AB primer.

In the process, the "first" AB primer hybridizes to the 3'-binding region of one target strand. The "A sub-section" of the AB primer is then digested by the enzyme having exonuclease activity to expose a primer binding site on the 3'-binding region of the target strand. The "third" ("short") primer A must then be capable of binding to this exposed binding site. This requires a sufficient degree of sequence homology between the "first" and "third" primers.

The Applicants maintain that the claims are not indefinite since the degree of homology must not be sufficiently different to prevent hybridization of the primers. Further, one skilled in the art would be able to readily determine the hybridization of the third and fourth primer to the second and third primers, respectively. Consequently, withdrawal of the rejections over claims 1-18 and 20-26 is requested.

Claim Rejections Under 35 USC §102

Claims 1-9, 13-18, and 20-26 were rejected under 35 USC 102(b) over Walker et al. (US 5,270,184, "the '184 patent"). The Applicants respectfully traverse this rejection. The present invention as recited in independent claims 1 and 20 includes 1) first and second strands that include digestion resistant regions remote from the 5' end, and 2) the use of an enzyme having 5' double stranded specific exonuclease activity

Two distinctions may be drawn between the present invention and the disclosure of the '184 citation. Firstly, the primers employed in the '184 patent do not include "digestion resistant" regions as required by claim 1 of the present application. Rather, the primers described in the '184 patent are "normal" primers and the reaction is conducted in the presence of a modified nucleotide (e.g. $dATP(\alpha S)$ (See column 5, lines 42-44 of the '184 patent). The effect is that the copy strand produced incorporates the modified nucleotide so that the restriction enzyme employed in the process can "nick" the "unmodified" strand (i.e. that produced by extension of the primer).

As a further note, with reference to Fig 2 of the '184 patent the S_1 primer with its recognition site binds to target sequence T_1 with an overhang so that T_1 may be extended in the 5'-3' direction to generate the semi-modified restriction site. In contrast, the "first" primer employed in the present invention binds fully to the target sequence. This has implications to the second point of distinction discussed below, namely, that the present invention includes an enzyme having 5' double stranded specific exonuclease activity.

Secondly, the '184 patent emphasizes that the enzyme system does <u>not</u> incorporate exonuclease activity in contrast to the present invention. In this respect the '184 patent references an strand displacement amplification method (SDA) see column 4, lines 61-62 that requires an exonuclease deficient form of klenow (exo klenow). (Id. col. 4, lines 61-62.) Additionally the '184 patent describes using the exo klenow at column 8, lines 59-60 and, particularly, at column 11, lines 1-6 referred to in the latest Office Action. More specifically, column 11, Walker states that "<u>importantly</u>, [the polymerase] should also <u>lack any 5'-3'</u> exonuclease activity. Polymerases, such as the ... exonuclease deficient klenow fragment of DNA polymerase I ... are useful." (the '184 patent, col. 11, lines 5-10, emphasis added.)

The reason for avoiding exonuclease activity in the '184 patent is that, if such activity were present, the copy produced by extension of the primer would simply be digested and could not be "nicked" with the restriction enzyme.

On page 3 of the Official Action, it was indicated that one enzyme having exonuclease activity is "exo-klenow DNA polymerase" (i.e. exo-). However, as noted above and as indicated from its name this is an exonuclease deficient enzyme.

For all of the reasons detailed above, it would seem the '184 patent does not anticipate (nor render obvious) independent claims 1 and 20 of the present application. Therefore, withdrawal of the rejections of Claims 1-9, 13-18, and 20-26 is requested.

Claim Rejections Under 35 USC 103

Claim 10 was rejected under 35 USC 103(a) over Walker et al. (the '184 patent) in view of Walker et al. (EP 0 500 224, "the '224 patent"). The '184 patent has been discussed above. The '224 patent has previously been discussed in the Response submitted on December 1, 2003, the substance which is incorporated here. Further, all that the '224 patent adds is the identification of an enzyme that has 5'-3' exonuclease activity, T7 gene 6 exonuclease. (Office Action, page 5.) It is respectfully submitted that to these two modify the method described in the '184 patent with the T7 gene 6 exonuclease identified in the '224 patent would render the gene application method of the '184 inoperable. The reason for avoiding exonuclease activity in the '184 patent is that, if such activity were present, the copy produced by extension of the primer would simply be digested and could not be "nicked" with the restriction enzyme. See the '184 patent, Fig. 1, the first two steps to produce the S₁-ext and the S₂-ext strands would be digested by the enzyme having 5'-3' exonuclease activity. This, in effect, prohibits further generation of sequences because the lack of the S₁-ext and the S₂-ext strands.

Therefore it is believed that the '184 patent can not be combined with the '224 patent. Consequently, withdrawal of the rejections of claim 10 is requested

In view of the foregoing remarks, Applicants respectfully submit that the cited references, either singly, or in combination, do not anticipate, or make obvious the claimed invention.

Accordingly, reconsideration leading to withdraw of all the rejections under 35 U.S.C. §§102(b) and 103(a) and passage of this application to issuance are respectfully requested. Additionally, the Examiner is invited to telephone the undersigned attorney if there are any questions about

this submission or other matters, which may be addressed in that fashion.

Respectfully submitted,

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